UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,661	07/20/2000	Marcel Linschoten	1103326 0631	9121

7470 7590 03/12/2004

WHITE & CASE LLP
PATENT DEPARTMENT
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 03/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,661	LINSCHOTEN ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 12-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,13,16 and 17* is/are rejected.

7)☒ Claim(s) *1-9,14,15 and 18-28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *13*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to amendments filed on 1/12/04. Applicant has amended claim 1. Claims 1-5 and 18 are compound claims. Claim 9, 13, 14, and 26 are composition claims. Claims 12, 16, and 17 are use claims. Claims 6-8, 19-25, and 28 are synthesis claims. Claims 15 and 27 concern a kit. The application concerns some pyridine mercapto carboxylic acid compounds, compositions, and uses thereof. This is the second action on the merits.

Response to Amendment

2. Applicants' incorporation of the assay method into the specification overcomes the objection made in point #7 of the previous office action. Applicants' amendments defining the substituents overcomes the indefiniteness rejections made in points #8 and #. Applicants' insertion of the appropriate definition from the specification of isostere overcomes the indefiniteness rejection made in point #10. Applicants amendment to claim 1, requiring the elected aromatic pyridyl group R_1 have an additional basic substituent overcomes the art-rejections over Mimura (JP 01254654 A2, CA document), Agfa-Gevaert (DE 3838467 A1, cited by Applicants), and Norcini ('259) and made in points #13-#15. The compounds taught by these references are all non-substituted pyridine compounds.

Election/Restrictions

3. Objection remains made to claims 1-9 and 11-28 as containing non-elected subject matter. The claimed compounds, compositions, and methods that employ them present a variable core. Formula I contains compounds drawn to the non-elected inventions to the extent it reads on compounds other than R_1 = pyridyl.

Title

4. The title of the invention is not descriptive after restriction. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: insertion of the phrase "Pyridine Mercapto Carboxylic Acid" at the beginning of the title.

These two objections will be considered together as Applicants make the same arguments about the scope of the claims. Applicants request that the non-elected subject matter be rejoined to the elected invention. They argue that after the amendments concerning prior art, discussed above, that formula (I) is now novel, and is therefor the special technical feature required by the international rules. This is not persuasive for three reasons. Firstly, the election was previously treated as an election without traverse (MPEP § 818.03(a)), since no effective traverse was made in Paper No. 10. Thus, Applicants have waived their right to petition the rejection. Secondly, rejoinder of non-elected invention is done only when the parent claim is allowable. Applicants were forced to amend their claim

to avoid prior art. Thus, no rejoinder is required. Thirdly, Applicants have already received a search on their elected pyridine compounds, which produced art. No second search can be done.

Claim Rejections - 35 USC § 112

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 12, 13, 16, and 17 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the pyridine mercapto carboxylic acid compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of

the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before cardiovascular disease occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning line 1, page 17 to line 5, page 18 lists the diseases Applicant intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical cardiovascular medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become diseased before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in cardiology with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of cardiovascular diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists

to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent cardiovascular generally. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing cardiovascular therapy and on the multitude of compounds embraced by Formula (I).

The Examiner suggests deletion of the word "prophylaxis" and the phrase "susceptible to".

Applicants make four arguments. Firstly, they proffer testing data to show that 40 of their compounds inhibit the enzyme carboxypeptidase U (CPU). Secondly, they assert that after reading such data "so too would the artisan find credible the assertion that such conditions could be prevented by administration of the instant compounds". Thirdly, they refer to lines 26-29, page 17 as to the diseases Applicants intend to prevent. The passage cited says, "[m]oreover, the compounds of the invention are expected to have utility in prophylaxis of re-occlusion and restenosis i.e. thrombosis) after thrombolysis, percutaneous trans-

luminal angioplasty (PTA) and coronary bypass operations; the prevention of re-thrombosis after microsurgery and vascular surgery in general." Fourthly, Applicants assert that re-occlusion, restenosis, and re-thrombosis are the diseases they really intend to prevent.

This is not persuasive. To the first point, Applicants supply no evidence that there is any correlation between the inhibition of CPU and the prevention of any disease. This is not an art-recognized correlation and Applicants do not assert that such a correlation exists. To the contrary, Boffa (Curr. Drug Targets) clarifies the speculative nature of clinical uses of such inhibitors in the last line of the abstract. Applicants are claiming prevention with the thousands of compounds embraced by Formula (I). Data on only forty species is hardly commensurate with the scope of the claims.

To the second point, assertion is not evidence. Applicants also mention, "prophylactic treatment of venous thrombosis and pulmonary embolism, arterial thrombosis (e.g. in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral merial thrombosis) and systemic embolism usually from the atrium during arterial fibrillation or from the left ventricle after transmural myocardial infarction". Do Applicants possess a method of predicting who will be subject to a

stroke or heart attack prior to the event, so they may receive Applicants compounds? Without such a method, prevention of these diseases is not possible.

To the third and forth points, Applicants claims are not limited to preventing the three conditions mentioned but rather to preventing all "conditions associated with inhibition of carboxypeptidase U", what ever they are. Restenosis, to name only one listed disease Applicants intend to prevent, or recurrent stenosis, is an extremely general term. Stenosis is the narrowing of any canal, orifice, valve, duct, tube (such as trachea), opening, etc. in the body. These can arise from obstructive lesions, deposits of granulations, organ hypertrophy, birth defects etc. There is no such thing as being able to treat, let alone prevent, such widely diverse problems that arise from different sources.

6. Claims 12, 13, 16, and 17 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating "conditions associated with inhibition of carboxypeptidase U". The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above. The issue concerns the correlation between the bio-assays discussed below and clinical efficacy for disease treatment.

a) Determining if any particular claimed compound would treat any particular carboxypeptidase U associated disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating carboxypeptidase U diseases is found in the passage spanning line 1, page 17 to line 5, page 18, which merely states Applicants' intention to do so. Applicants describe formulations in the passage spanning line 7, page 15 to line 23, page 16. Doses required to practice their invention are taught in lines 25-29, page 16. A 10,000-fold range of doses is proposed. Since no carboxypeptidase U inhibitor has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? Since no testing data is provided how is this dose to be calculated? There is an *in vitro* assay mentioned in lines 19-24, page 18. No data is provided and it is unclear if this assay is correlated to clinical treatment of any human diseases. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in carboxypeptidase U related diseases is provided by

Boffa (Curr. Drug Targets) who clarifies the speculative nature of clinical uses of such inhibitors in the last line of the abstract.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the unknown list of diseases embraced by the term "conditions associated with inhibition of carboxypeptidase U". Thus, the scope of claims is very broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants argue that the data on the forty compounds discussed above provides the require enablement for disease treatment and again asserts that " in light of the data, one of skill in the art would find credible the assertion that the instant compounds would be effective in the treatment of any condition associated with inhibition of carboxypeptidase U." This is not persuasive for three reasons. Firstly, the reverence previously cited says that no diseases are so art-recognized. Secondly, thousands of diverse compounds are presently claimed to be so active. Compounds 1, 3, 4, 10-13, 15, 16, and 34 are not even the pyridine compounds presently being examined. The most potent pyridine compound is Example 6. The least potent is Example 8. These two compounds differ by 1,000-fold in their ability to inhibit CPU. Yet the only difference between the two compounds is the presence of an ethyl group on 8, which is not present on 6. Since such minor changes make such profound impact on the biological activity, it is not scientifically credible that the data on thirty pyridine compounds provides enablement even for enzyme inhibition, for the broadly diverse thousands of compounds of Formula I. It is even less credible, that these thousands of compounds will affect the disease treatments presently claimed. Thirdly, the claims are not even limited to the diseases named in the specification but included

hundreds of conditions which cause inhibition of CPU as well as those only indirectly associated with the clotting of blood.

7. Claims 12, 13, 16, and 17 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "conditions associated with inhibition of carboxypeptidase U". It is unclear what diseases and treatments applicant is intending to encompass. Associated can either be cause or effect. Associated can mean either directly or secondarily. Since the enzyme is involved in blood-clotting, would hemophilia be such a diseases? Does leukemia have some association, however small, with CPU? Determining whether a given disease responds or does not respond to such a enzyme inhibitor and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

Conclusion

8. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public

PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

9. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact Mukund Shah SPE of 1624 at (571)-272-0674.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK